

## REMARKS

Applicants have studied the Office Action of December 14, 2004 ("Office Action"). It is respectfully submitted that the application is in condition for allowance. Prior to entry of the present amendment, claims 1-21 were pending in the present application, and had all been rejected. Claims 1, 4-8 and 14 have been amended by virtue of the present amendment; claims 2, 9, 19 and 21 have been canceled; and new claims 22-24 have been added. No new matter has been added. Allowance and reconsideration of the application in view of Applicants' amendment and the ensuing remarks are respectfully requested.

Claim 1 has been amended to more particularly describe that which Applicants regard as their invention. Claim 1, as amended, describes "*a cell culture matrix composition,*" including a tissue powder that is derived from a "*full and intact*" whole organ, whole tissue, or portion thereof. Moreover, "*the organ is a liver, a lung, a kidney, a pancreas, a spleen, a testis, an intestinal wall, an adrenal gland, a thyroid gland, a parathyroid gland, an ovary or a brain, and the tissue is skin, muscle, a blood vessel wall or bone marrow.*" Support for this amendment may be found throughout the Specification; for instance, at page 4, line 30 through page 5, line 6, and at page 5, lines 14-23.

Claim 4 has been amended to more particularly describe that which Applicants regard as their invention. Claim 4, as amended, describes "*a method for producing a tissue powder,*" including isolating a biological material selected from a "*full and intact*" whole organ, whole tissue, or portion thereof. Moreover, "*the biological material is a liver, a lung, a kidney, a pancreas, a spleen, a testis, an intestinal wall, an adrenal gland, a thyroid gland, a parathyroid gland, an ovary or a brain, and the tissue is skin, muscle, a blood vessel wall or bone marrow.*" Support for this amendment may be found throughout the Specification; for instance, at page 4, line 30 through page 5, line 6, and at page 5, lines 14-23.

Claim 5 has been amended to more particularly describe that which Applicants regard as their invention. Claim 5, as amended, describes the "*converting*" set forth in claim 4 to include "*grinding the biological material to produce the tissue powder.*" This claim has also been amended to include "*said*" with reference to "*converting the biological material*" to provide more clear antecedent basis for this term. Support for this amendment may be found throughout the Specification; for instance, at page 6, lines 23-29.

Claim 6 has been amended to more particularly describe that which Applicants regard as their invention. Claim 6, as amended, adds a “*sonicating*” procedure to the method set forth in claim 4, including “*sonicating the tissue powder to produce a quantity of finer particles.*” Support for this amendment may be found throughout the Specification; for instance, at page 6, lines 23-29.

Claim 7 has been amended to more particularly describe that which Applicants regard as their invention. Claim 7, as amended, refers to sonicating the “*tissue powder*” with a sonic dismembrator. This claim has also been amended to include “*said*” with reference to “*sonicating the tissue powder*” to provide more clear antecedent basis for this term. Support for this amendment may be found throughout the Specification; for instance, at page 6, lines 23-29.

Claim 8 has been amended to more particularly describe that which Applicants regard as their invention. Claim 8, as amended, adds a “*soaking*” procedure to the method set forth in claim 4, prior to “*sonicating the tissue powder.*” Support for this amendment may be found throughout the Specification; for instance, at page 6, lines 23-29.

Claim 14 has been amended to more particularly describe that which Applicants regard as their invention. Claim 4, as amended, describes a method, which includes suspending cells in a medium that includes a tissue powder derived from a biological material selected from a “*full and intact*” whole organ, whole tissue, or portion thereof. Moreover, “*the biological material is a liver, a lung, a kidney, a pancreas, a spleen, a testis, an intestinal wall, an adrenal gland, a thyroid gland, a parathyroid gland, an ovary or a brain, and the tissue is skin, muscle, a blood vessel wall or bone marrow.*” Support for this amendment may be found throughout the Specification; for instance, at page 4, line 30 through page 5, line 6, and at page 5, lines 14-23.

New claim 22 has been added, and describes an embodiment of the present invention wherein the cells in the method of claim 14 are “*of a different type than those which at least partially constitute the biological material.*” While cells may exhibit “*optimal growth and differentiation*” when they are cultured in a matrix derived from the same organ or tissue with which they are typically associated, alternate embodiments of the invention provide for the culturing of cells in matrices derived from different organs and/or tissues. Support for this amendment may be found throughout the Specification; for instance, at page 5, lines 7-13.

New claim 23 has been added, and describes a “*cell culture matrix composition*” including a “*fine tissue powder*” derived from a “*full and intact*” whole organ, whole tissue, or

portion thereof. Moreover the *“fine tissue powder”* is produced by grinding and sonicating procedures. Support for this new claim may be found throughout the Specification; for instance, at page 5, lines 24-28.

New claim 24 has been added, and describes a *“cell culture matrix composition”* including a tissue powder that is derived from a *“full and intact”* whole liver or a portion thereof, and a medium. Support for this new claim may be found throughout the Specification; for instance, at page 7, line 27 through page 8, line 18.

Examiner rejected claims 1-21 under 35 U.S.C. § 112, second paragraph. Specifically, Examiner found these claims to be vague and indefinite, their metes and bounds being unclear, *“for recitation of ‘a portion of a whole organ or a portion of a whole tissue’ since it is unclear what portion of the organ or tissue is intended, or is it an amount which is intended?”* Examiner further found that claims 5-6 lack clear antecedent basis for the term *“converting,”* noting that *“it is uncertain whether the converting recited in these claims is a separate converting step than what is being performed in claim 4.”* Examiner suggested inserting *“said”* before *“converting”* at appropriate points in claims 5-6. Examiner additionally concluded that *“claim 4 is unclear since it is uncertain how the tissue powder is obtained by ‘converting’,”* and inquired, *“[h]ow is the step of ‘converting’ being carried out per se?”* Examiner additionally found that *“claim 7 is lacking of clear antecedent basis for the recitation of the term ‘sonicating’,”* and suggested inserting *“said”* before *“sonicating”* in this claim. Examiner also found that, in claim 8, *“it is unclear how ‘the tissue powder’ . . . is obtained for soaking since sonicating is a technique used to obtain ‘the tissue powder’ by sonicating the ground particles.”* Finally, Examiner found claim 14 to be *“unclear for recitation of ‘supporting cell growth’ since it is unclear whether this is intended to mean merely a suspension culture medium or whether it is intended to mean an organ matrix for transplantation or as an organ replacement.”* With respect to claims 2, 9, 19 and 21, which have been canceled by virtue of the present amendment, these rejections are rendered moot. With respect to the remaining claims, however, these rejections under 35 U.S.C. § 112, second paragraph, are respectfully traversed.

First, Applicants respectfully submit that the term *“a portion of a whole organ or a portion of a whole tissue”* is neither vague nor indefinite. In fact, Applicants’ Specification clearly describes what is intended by the use of this term.

The term “whole,” when used with reference to the organs and tissues included in various embodiments of the present invention, denotes the fact that these biological materials are not decellularized or otherwise digested prior to being processed into support matrices. Instead, such organs and tissues are processed in an undigested form. Moreover, use of the term “whole” is not intended to imply that a full and intact organ is necessarily processed; indeed, in many embodiments of the present invention only a **portion** of an organ is used to produce a matrix. By way of example, a segment of an intestine or a piece of skin may be utilized, just as a full, intact liver might be used. However, in each embodiment, the “whole” organ, tissue or portion thereof is processed in undigested form, whether the organ is a full and intact organ or tissue, or only a portion thereof. See Specification at p.5, lines 14-23 (emphasis added).

As specifically set forth in the Specification, “a portion of a whole organ or a portion of a whole tissue” does, in fact, refer to an amount of the whole organ or whole tissue. The term “portion” is used to differentiate between a “full and intact” organ and a lesser amount thereof (e.g., a segment of an intestine, a piece of skin, etc.). Each of Applicants’ independent claims has been amended to include the language “full and intact” to more clearly delineate the meaning of this term. Applicants therefore respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, second paragraph.

Second, Applicants have adopted Examiner’s suggestion to include the word “said” before “converting” at an appropriate point in claim 5, and have amended claim 6 to no longer include any reference to “converting.” With regard to Examiner’s inquiry as to how the step of “converting” is accomplished, Applicants respectfully submit that this is an improper inquiry for purposes of 35 U.S.C. § 112, second paragraph. Indeed, “[t]he essential inquiry pertaining to this requirement is whether the claims set out and circumscribe a particular subject matter with a reasonable degree of clarity and particularity” (MPEP § 2173.02; emphasis added). Furthermore, “[b]readth of a claim is not to be equated with indefiniteness” (MPEP § 2173.04, citing *In re Miller*, 441 F.2d 689, (CCPA 1971)). A proper inquiry under 35 U.S.C. § 112, second paragraph, does not focus on how converting is accomplished, rather it focuses on whether the term “converting,” when read in context with the remainder of the claim, describes the claimed subject matter with a reasonable degree of clarity and particularity. Applicants submit that the skilled artisan could readily ascertain the meaning of the term “converting” based on its use in the context of the claim: “converting” refers to the alteration of the biological

material from one thing to another; in this case, from a whole organ, tissue or portion thereof to a tissue powder.

Furthermore, Applicants respectfully direct Examiner to the following passage from the Specification:

The resulting freeze-dried organ, tissue or portion thereof (whether reduced to smaller pieces or not) is next converted into powder. This may be achieved, for example, by grinding with a mortar and pestle. The powder may then be soaked in a culture medium and sonicated using a sonic dismembrator to further reduce the powder into finer particles. Other methods known in the art and comparable to those described may be used in the alternative. Due to the lyophilization (freeze-drying) undergone by the powder in one embodiment of the present invention, it may be stored for future use without losing its potency. See Specification at p.6, lines 23-29 (emphasis added).

There are a number of techniques that may be readily used to convert the whole organ, tissue or portion thereof of the invention into a powder. Applicants enumerate several means for accomplishing this, including the use of grinding and sonicating procedures; particular applications of which are set forth in claims 5 and 6.

Still further, Applicants submit that one of skill in the art would have no difficulty discerning the meaning of this term in the context of the claim based on its normal use. For instance, a conventional dictionary definition of “*converting*” (found in Merriam-Webster’s OnLine dictionary) is “*to alter the physical or chemical nature or properties of especially in manufacturing.*”

“*Converting*” is not an unusual term to understand. It has a clear meaning in the context of the claim, in the Specification, and in a conventional dictionary. Thus, the term “*converting*” is sufficiently clear so as to describe the subject matter of the claim with reasonable particularity and distinctness, and is therefore sufficiently clear and definite for purposes of 35 U.S.C. § 112, second paragraph. Applicants respectfully request reconsideration and withdrawal of this rejection.

Third, Applicants have adopted Examiner’s suggestion to include the word “*said*” before “*sonicating*” at an appropriate point in claim 7. Applicants therefore respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, second paragraph.

Fourth, claim 8, as well as claims 5 and 6, from which it depends, has been amended to clarify the nature of the inventive method. The tissue powder is produced by grinding the

biological material, and a quantity of finer particles is produced by sonicating the tissue powder. Claim 8 describes that the tissue powder may be soaked in a culture medium prior to sonication. Applicants respectfully submit that the amendments to the aforementioned claims render them sufficiently definite, and therefore request reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, second paragraph.

Finally, Applicants have amended claim 14 such that it no longer includes any reference to “*supporting cell growth.*” Applicants note, however, that the inventive matrix may indeed be used to support cell growth in a suspension culture medium, to support cell growth in an organ matrix for transplantation or as an organ replacement, or for other purposes that the skilled artisan can routinely implement. However, in light of their amendment to claim 14, Applicants respectfully submit that this claim is sufficiently definite, and therefore request reconsideration and withdrawal of this rejection under 35 U.S.C. § 112, second paragraph.

Examiner rejected claims 1-3 under 35 U.S.C. § 102(b) as being anticipated by Brekke *et al.* (U.S. Pat. No. 5,855,608; hereinafter “Brekke”) and Badylak *et al.* (U.S. Pat. No. 5,516,533; hereinafter “Badylak”). Examiner found that Brekke and Badylak each teach “*a cell culture matrix composition comprising a tissue powder such as bone and the composition further comprising a medium.*” With respect to claim 2, which has been canceled by virtue of the present amendment, this rejection is rendered moot. With respect to the remaining claims, this rejection is respectfully traversed.

A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference (MPEP § 2131 (citing Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631 (Fed. Cir. 1987))).

Brekke describes an implantable polymeric structure configured to support the re-growth of two different tissue types. In a preferred embodiment, the two types are cartilage and subchondral bone; the device may thus be used to facilitate healing of a human joint. Reference is briefly made to bone powder in Brekke in connection with the patent applicants’ criticism of inferior prior art mechanisms for joint repair (Col. 1, line 66 to Col. 2, line 4). Indeed, the disclosure of Brekke is limited to a media based on an RGD attachment moiety of fibronectin for supporting cell growth in the implantable polymeric structure (Col. 11, lines 29-38).

Brekke does not describe the cell culture matrix composition of the present invention as set forth in independent claim 1, as amended and from which claim 3 depends. Specifically, Brekke does not describe a tissue powder derived from one of the types of whole organ or tissue enumerated in Applicants' independent claim 1. The fibronectin-based media is entirely unrelated (*i.e.*, it is not based on a tissue powder), and Brekke's disapproving reference to bone powder can not be said to anticipate the claimed invention. There is no indication that the bone powder referred to by Brekke is derived from a "*full and intact whole organ*," as is required by Applicants' independent claim 1, and even assuming *arguendo* that the bone powder was derived from a whole organ or tissue, which Applicants in no way concede, it is not derived from one of the whole organs or tissues enumerated in claim 1. Therefore, Brekke does not anticipate Applicants' independent claim 1, and claim 3 that depends therefrom.

Badylak describes a tissue graft composition including certain fluidized intestinal submucosa; specifically, "*the tunica submucosa along with the lamina muscularis mucosa and the stratum compactum of a segment of small intestine, said layers being delaminated from the tunica muscularis and the luminal portion of the tunica mucosa of said segment*" (Col. 2, lines 30-35). The particular layers of the segment of small intestine are obtained by mechanically wiping them from the segment of intestine (Col. 2, lines 39-43). Indeed, these layers are merely a few of the many layers that comprise the small intestine. This is plainly described in U.S. Patent No. 4,902,508, which is specifically incorporated by reference in Badylak for the purpose of describing the process of obtaining only certain layers from a segment of small intestine (Col. 3, lines 26-31 and 53-61, and Fig. 1 of the '508 patent). Specifically, as described in Badylak and the '508 patent to which it refers, a segment of intestine includes seven layers (illustrated as A-G in Fig. 1 of the '508 patent); however, the compositions of Badylak include only three of these seven layers.

Badylak does not describe the cell culture matrix composition of the present invention as set forth in Applicants' independent claim 1, as amended and from which claim 3 depends. The compositions of Applicants' invention, as claimed, are based on a tissue powder derived from a full and intact whole organ, tissue or portion thereof. The layers of intestinal submucosa described in Badylak are clearly neither a full and intact whole organ nor a full and intact whole tissue. Furthermore, the select submucosa of Badylak are not a "*portion*" of a full and intact whole organ or tissue, as that term is used in Applicants' invention. In fact, the term "*portion*"

has a specific connotation in the present application. It refers not to particular anatomical components of an organ or tissue, such as only three out of seven layers of the small intestine, but rather to a piece or segment of the whole organ or tissue, such as “*a segment of an intestine*” (See Specification at p.5, line 20). Badylak specifically indicates that it is based on three of seven layers of a “*segment of small intestine,*” while Applicants’ claims require the whole segment. Therefore, Badylak does not anticipate Applicants’ independent claim 1, and claim 3 that depends therefrom, as it does not describe the inventive tissue powder.

In light of the foregoing remarks, Applicants respectfully submit that neither Brekke nor Badylak anticipates claims 1 or 3, and therefore request reconsideration and withdrawal of this rejection under 35 U.S.C. § 102(b).

Examiner rejected claims 4-5, 9, 11 and 13 under 35 U.S.C. § 102(b) as being anticipated by Badylak. Specifically, Examiner found that Badylak teaches “*a method for producing tissue powder comprising isolating tissue or organ as a biological material and converting it to tissue powder.*” Examiner further found that Badylak teaches grinding material obtained from the small intestine, freezing it, and reducing it into smaller pieces. With respect to claim 9, which has been canceled by virtue of the present amendment, this rejection is rendered moot. With respect to the remaining claims, this rejection is respectfully traversed.

Badylak does not describe the method for producing tissue powder of the present invention as set forth in independent claim 4, as amended and from which the remaining rejected claims depend, for reasons similar to that described above with respect to Applicants’ claim 1. In short, Badylak does not describe a full and intact whole organ, tissue or portion thereof, as is required by Applicants’ independent claim 4. Badylak specifically indicates that it is based on three of seven layers of a “*segment of small intestine,*” while Applicants’ claims require the whole segment. Therefore, Badylak does not anticipate Applicants’ independent claim 4, and the remaining rejected claims that depend therefrom.

In light of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 102(b).

Examiner rejected claims 14-16 and 19-21 under 35 U.S.C. § 102(b) as being anticipated by Brekke. In particular, Examiner found that Brekke teaches “*a method of supporting cell*



*growth comprising providing cells and suspending cells in a medium with a tissue powder derived from biological material.*” With respect to claims 19 and 21, which have been canceled by virtue of the present amendment, this rejection is rendered moot. With respect to the remaining claims, this rejection is respectfully traversed.

Brekke does not describe the method of the present invention as set forth in independent claim 14, as amended and from which the remaining rejected claims depend, for reasons similar to that described above with respect to Applicants’ claim 1. In short, Brekke does not describe a tissue powder derived from one of the types of whole organ or tissue enumerated in Applicants’ independent claim 14. Therefore, Brekke does not anticipate Applicants’ independent claim 14, and the remaining rejected claims that depend therefrom.

In light of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 102(b).

Examiner rejected claims 1-21 under 35 U.S.C. § 103(a) as being rendered obvious by Brekke in view of Badylak, Weiss *et al.* (U.S. Pat. No. 6,497,872; hereinafter “Weiss”) and Vail *et al.* (U.S. Pat. No. 4,663,295; hereinafter “Vail”). Specifically, Examiner found that “[Weiss] teach[es] perfusion technique,” and “[Vail] teach[es] sonicating techniques,” and that “[i]he claims differ from [Brekke] in that sonicating techniques nor perfusion technique are clearly disclosed.” With respect to claims 2, 9, 19 and 21, which have been canceled by virtue of the present amendment, this rejection is rendered moot. With respect to the remaining claims, however, this rejection is respectfully traversed.

Three basic criteria must be met to establish a prima facie case of obviousness: (1) “*there must be some suggestion or motivation . . . to combine reference teachings,*” (2) “*there must be a reasonable expectation of success,*” and (3) the prior art references “must teach or suggest all the claim limitations.” MPEP § 2142 (emphasis added).

For the reasons set forth above, neither Brekke nor Badylak teach or suggest all of the claim limitations, as amended. Neither reference describes the inventive compositions or methods. One notes the existence of bone powder, which is not derived from one of the enumerated sources in Applicants’ claims, and the other teaches the use of layers of an intestine that are less than a “*portion*” of a full and intact whole organ as described in Applicants’ claims. Applicants agree with Examiner that, in addition to these shortcomings, neither Brekke nor

Badylak describes the use of perfusion or sonication techniques. However, while Applicants in no way concede that Examiner's combination of references is proper herein, even if the combination is proper, the cited combination of references -- supplementing the aforementioned references with information regarding perfusion and sonication techniques -- still does not teach or suggest all of the limitations of Applicants' claims.

In light of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of this rejection under 35 U.S.C. § 103(a).

All of the claims remaining in the application are now believed to be allowable. Favorable consideration and a Notice of Allowance are earnestly solicited. If for any reason Examiner finds the application other than in condition for allowance, Examiner is requested to call the undersigned attorney at the Los Angeles telephone number (213) 633-6800 to discuss the steps necessary for placing the application in condition for allowance.

Respectfully submitted,  
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